

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



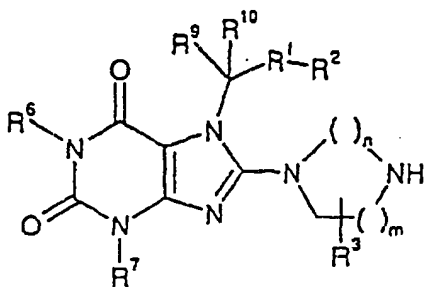
(43) International Publication Date
10 January 2002 (10.01.2002)

PCT

(10) International Publication Number
WO 02/02560 A3

- (51) International Patent Classification⁷: A61K 31/522, C07D 473/04, 473/06, 473/08
- (21) International Application Number: PCT/DK01/00467
- (22) International Filing Date: 4 July 2001 (04.07.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
PA 2000 01040 4 July 2000 (04.07.2000) DK
60/223,240 4 July 2000 (04.07.2000) US
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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: 25 April 2002
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PURINE-2,6-DIONES WHICH ARE INHIBITORS OF THE ENZYME DIPEPTIDYL PEPTIDASE IV (DPP-IV)



(57) Abstract: The present invention relates to therapeutically active and selective inhibitors of the enzyme DPP-IV, pharmaceutical compositions comprising the compounds and the use of such compounds for and the manufacture of medicaments for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity, as well as methods for treating diseases that are associated with proteins which are subject to inactivation by DPP-IV, such as type 2 diabetes and obesity.

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/DK 01/00467

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/522 C07D473/04 C07D473/06 C07D473/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X

DATABASE STN INTERNATIONAL [Online]
 04-07-2000 - 04-07-2001,
 retrieved from FILE REGISTRY
 XP002902159
 see RN 335403-13-9, 333755-39-8,
 333755-22-9, 333305-42-3, 333305-36-5,
 333305-27-4, 333305-05-0, 332905-08-05,
 332904-76-4, 332384-40-4, 332098-96-1,
 331671-66-0, 331671-64-8,
 329702-29-6, 318271-92-0, 313396-00-8,
 313274-01-0,
 313274-00-9, 313230-36-3, 304876-71-9, 303972
 -96-5, 302777-00-0
 abstract

1,4-19,
 21,
 27-44,
 46-54

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Date of the actual completion of the international search

12 November 2001

Date of mailing of the international search report

25.02.2002

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Inter national Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DATABASE STN INTERNATIONAL [Online] 04-07- 2000 - 04-07-2001, retrieved from FILE REGISTRY, RN XP002902160 331841-51-1, 313554-09-5, 313530-91-5, 313530-90-4, 313273-71-1, 313255-35-5, 312915-48-3, 303973-85-5, 303973-23-1, 303971-30-4, 302800-67-5, 302777-10-2, 300391-56-4, 299421-57-1, 299419-33-3,	53
P,A	---	1
X	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1987:95577, Document no. 106:95577, ROMANENKO N I ET AL: "Synthesis and biological activity of 3-methyl, 7-or 8-alkyl-, 7,8-dialkyl, heterocyclic, and cyclohexylaminoxanthines " XP002902161 abstract & FARM. ZH. , vol. 5, 1986, pages 41-44, Kiev	53
A	---	1
X	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1970:55410, document no. 72:55410, K H KLEINE ET AL: "Synthesis of substituted bisxanthines" XP002902162 abstract & ARZNEIM. -FORSCH. , vol. 19, no. 11, 1969, pages 1854-1855, XP002902162	53
A	---	1
X	DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1969:459503, KUBOTA, KAZUHIKO ET AL: "Pharmacological studies of basic theophylline derivatives. I Effects on the cardiovascular system" XP002902163 document no. 71:59503 abstract & YAKUGAKU ZASSHI, vol. 89, no. 4, 1969, pages 441-445,	53
A	---	1
	--- -/--	

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/DK 01/00467

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1986:626150, , SAMURA B A ET AL: "Synthesis, neurotropic and diuretic activity of 7,8-disubstituted 3-methylxanthines" XP002902164 document no. 105:226150 abstract & KHIM. -FARM. ZH. , vol. 20, no. 1, 1986, pages 52-55,</p>	53
A	---	1
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1975:80351, document no. 82:80351, GORCZYCA M ET AL: "Piperazine derivatives of methylxanthines. I. Chemical and pharmacological properties of 8-piperazinotheophyllines" XP002902165 abstract & FARMACO, ED. SCI. , vol. 29, no. 10, 1974, pages 802-810,</p>	53
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1999:559580, HANS ZIMMER ET AL: "Synthesis of 8-substituted xanthines and their oxidative skeleton rearrangement to 1-cxo-2,4,7,9-tetraazaspiro (4,5)dec-2-ene-6,8,10-triones" XP002902166 document no. 131:351159 abstract & EUR. J. ORG. CHEM. , vol. 9, 1999, pages 2419-2428,</p>	53
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1977:139992, GUTOROV L A ET AL: "1,8-Disubstituted derivatives of theobromine and their pharmacological activity" XP002902167 document no. 86:139992 abstract & KHIM. FARM. ZH. , vol. 10, no. 12, 1976, pages 61-64,</p>	53

	-/--	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 01/00467

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1978:509376, CYGANKIEWICS A ET AL: "Piperazine derivatives of dimethylxanthines. V. Preparation and properties of 8-piperazino- and 1- beta.-hydroxypropyl-8-piperazinotheobromin es" XP002902168 document no. 89:109376 abstract & ACTA POL. PHARM., vol. 34, no. 6, 1977, pages 607-612, ---</p>	53
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1998:260235 , KHALIULLIN F A ET AL: "Synthesis of biologically active derivatives of xanthine and benzimidazole" XP002902169 document no 129:49337 abstract & BASHK. KHIM. ZH., vol. 4, no. 4, 1997, pages 59-62, ---</p>	53
X	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1987:400259, MARTINSON E A ET AL: "Potent adenosine receptor antagonists that are selective for the A1 receptor subtype" XP002902170 document no. 107:259 abstract & MOL. PHARMACOL., vol. 31, no. 3, 1987, pages 248-252, ---</p>	53
A	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1989:586916, SKUL'SKAYA E A ET AL: "Properties and pharmacological action of derivatives of 7,8-disubstituted 3-methylxanthine and 6H-8-methylimidazo (1,2-f)xanthine" XP002902171 document no. 111:186916 abstract & FARM. ZH., vol. 4, 1989, pages 34-39, Kiev ---</p>	1-54

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INTERNATIONAL SEARCH REPORT

Intr tional Application No
PCI/DK 01/00467

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1997:297890, MAZUR I A ET AL: "Synthesis and antiphlogistic effect of some 7-substituted 8-(3,5-dimethyl-1- pyrazolyl) theophyllines" XP002902172 document no. 126:330513 abstract & FARM. ZH. , vol. 3, 1996, pages 82-84, Kiev</p>	1-54
A	<p>DATABASE STN INTERNATIONAL [Online] File CAPLUS, CAPLUS; accession no. 1983:539617, GORCZYCA MARIA ET AL: "Synthesis and properties of 7- and 8-piperaziny derivatives of theophylline" XP002902173 document no. 99:139617 abstract & ACTA POL. PHARM., vol. 39, no. 5-6, 1982, pages 315-321,</p>	1-54
A	<p>WO 91 07945 A (LVMH RECH) 13 June 1991 (1991-06-13) the whole document</p>	1-54
A	<p>WO 92 05175 A (BEECHAM GROUP PLC) 2 April 1992 (1992-04-02) the whole document</p>	1-54

SA 035268

INTERNATIONAL SEARCH REPORT

Information on patent family members

01/10/01

International application No.

PCT/DK 01/00467

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9107945	A1	13/06/91	AT	119027 T	15/03/95
				AU	650250 B	16/06/94
				AU	6745990 A	26/06/91
				DE	502043 T	25/02/93
				DE	69017467 D,T	19/10/95
				EP	0502043 A,B	09/09/92
				ES	2071836 T	01/07/95
				FR	2654935 A,B	31/05/91
				JP	5504129 T	01/07/93
				US	5470579 A	28/11/95
WO	9205175	A1	02/04/92	AU	653364 B	29/09/94
				AU	8541391 A	15/04/92
				CA	2092430 A	27/03/92
				EP	0550570 A	14/07/93
				GB	9020959 D	00/00/00
				IE	913350 A	08/04/92
				JP	6501251 T	10/02/94
				MX	9101237 A	04/05/92
				NZ	239921 A	23/12/93
				PT	99062 A	31/08/92
				ZA	9107610 A	30/09/92